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Behavioral Toxicity of Trialkyltin Compounds: A Review

Lawrence W. Reiter and Patricia H. Ruppert

Neurotoxicology Division
US Environmental Protection Agency
Research Triangle Park, NC

Send correspondence to:

Dr. Lawrence W. Reiter
Neurotoxicology Division (MD 74B)
US Environmental Protection Agency
Research Triangle Park, NC 27711
(919)541-2671

HEALTH EFFECTS RESEARCH LABORATORY
OFFICE OF RESEARCH AND DEVELOPMENT
U.S. ENVIRONMENTAL PROTECTION AGENCY
RESEARCH TRIANGLE PARK, NC 27711

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Triethyltin (TET) and trimethyltin (TMT) are neurotoxic organotin compounds which produce different patterns of toxicity in adult animals. Exposure to TET produces behavioral toxicity (decreased motor activity, grip strength, operant response rate and startle response amplitude) which reflects impaired neuromotor function. These deficits are consistent with the reported myelin vacuolation and cerebral edema produced by TET, and with its direct effects on muscle. Exposure to TMT produces both hyperactivity and impaired learning and performance. These impairments are consistent with reported neuronal cell death produced by TMT, particularly in limbic system structures. While the behavioral deficits produced by repeated exposure to TET are reversible when dosing is terminated, the behavioral impairment produced by a single exposure to TMT appears to be irreversible.

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ABSTRACT

Triethyltin (TET) and trimethyltin (TMT) are neurotoxic organotin compounds which produce different patterns of toxicity in adult animals. Exposure to TET produces behavioral toxicity (decreased motor activity, grip strength, operant response rate and startle response amplitude) which reflects impaired neuromotor function. These deficits are consistent with the reported myelin vacuolation and cerebral edema produced by TET, and with its direct effects on muscle. Exposure to TMT produces both hyperactivity and impaired learning and performance. These impairments are consistent with reported neuronal cell death produced by TMT, particularly in limbic system structures. While the behavioral deficits produced by repeated exposure to TET are reversible when dosing is terminated, the behavioral impairment produced by a single exposure to TMT appears to be irreversible.

INTRODUCTION

To a limited extent, the neurotoxicity of both inorganic and organic tin compounds has been recognized for many years. In the early 19th century, Orfila described muscular weakness, loss of pain sensation and immobility in dogs exposed to tin chloride (Kimbrough, 1976). In 1881, White reported that vapors of triethyltin acetate produced headaches, general weakness, nausea and diarrhea. The following quote from Sollmann's (1906) textbook on pharmacology refers to the report of White and recognizes that the CNS is a principal target organ for tin compounds:

> "This metal is absorbed in part even from non-corrosive preparations...The symptoms on injection devolve to some extent on the central nervous system, as stimulation and subsequent paralysis...With more chronic poisoning the gastroenteritis is most marked, but there is also an ataxia and motor paralysis, resembling chronic lead-poisoning (White,1880)".

The present review will focus on the behavioral toxicity of the alkyltin compounds. Since the major research emphasis has been on the trialkyltins, and more specifically on triethyltin (TET) and trimethyltin (TMT), we will review and contrast the behavioral effects of these two

compounds.

SIGNS AND SYMPTOMS OF POISONING IN HUMANS

The signs and symptoms associated with human exposure to TET and TMT are summarized in Table 1.

An extensive episode of TET poisoning occurred in France in the 1950's resulting from the contamination of Stalinon, a proprietary preparation used in the treatment of skin infections (for review see Barnes and Stoner, 1959). Stalinon capsules, which contained diethyltin and linoleic acid, were contaminated with monoethyltin and TET. Of the 217 people reportedly poisoned by this preparation, 100 died.

Occupational exposures have accounted for two reported episodes of TMT poisoning. The first episode involved two chemists who were synthesizing dimethyltin and were inadvertently exposed to vapors of dimethyl- and trimethyltin chloride for approximately 3 months (Fortemps et al., 1978). The second episode involved twenty-two chemical workers who were exposed to both dimethyl- and trimethyltin dichloride and methyl bromide due to a malfunctioning ventilation system (Ross et al., 1981). Since some of the non-specific signs and symptoms of toxicity in humans overlap between TET and TMT, the toxicity of these two compounds was generally thought to be

qualitatively similar, differing only in relative potency. In retrospect, however, while certain symptoms are common to both compounds (e.g., headaches, pain, loss of weight/appetite), there are important differences in the overall clinical syndrome. TET toxicity reflects primarily a sensorimotor deficit while TMT reflects specific behavioral impairment. As we know now, these differences in symptoms reflect marked differences in the underlying neurotoxicity associated with exposure to these two compounds.

SIGNS OF POISONING IN ANIMALS

Stoner et al. (1955) described the acute toxicity resulting from organotin exposure in animals. TET was the most potent, although other alkyltins produced similar signs of poisoning. Muscle weakness was observed within hours after dosing; following a short period of recovery, tremors developed, leading to convulsions and death 2-5 days after dosing. Tremors were more pronounced after exposure to TMT; aggressive sparring with cage mates was also observed (Stoner et al., 1955; Barnes and Stoner, 1958). Even in recent reports, the acute toxicity of TET and TMT has been described as being qualitatively similar: trembling, irritation, twitching, loss in body weight and progressive paralysis (Tan and Ng, 1977). The apparent similarity in

signs of poisoning between TET and TMT during the acute phase of toxicity led these compounds to be classified as general examples of alkyltin intoxication.

Although increased water content of the brain and spinal cord was observed with TET and not TMT (Barnes and Stoner, 1958), the neuronal damage produced by TMT within the limbic system was not described until recently (Brown et al., 1979). Behavioral studies have clearly differentiated between the neurotoxicity of TET and TMT. Tables 2 and 3 summarize behavioral studies of TET and TMT toxicity, respectively. Although toxicity produced by TET becomes more pronounced with continued exposure, reversal of behavioral deficits occurs within weeks after termination of dosing. In contrast, following acute exposure to TMT, toxicity progresses from acute effects, through a period of hyperreactivity characterized by tail mutilation, vocalization and seizures (Dyer et al., 1982), to a stage where overt signs of poisoning are no longer evident but behavioral deficits persist. These differences in long-term toxicity have led to different strategies for the assessment of behavioral impairment. Evaluations of TET have generally focussed on repeated testing throughout the period of dosing, followed by a recovery period. Evaluations of specific behavioral impairments produced by TMT have generally focussed on testing weeks to months after a single injection.

BEHAVIORAL EFFECTS OF TET

TET produces primarily a neuromotor impairment which is reversible. Following subacute administration of 5 or 10 ppm TET in the drinking water, decreases in locomotor activity were seen in figure-eight mazes (Reiter et al., 1980); within 2 weeks after removal of TET from the drinking water, the motor activity of TET-exposed animals had returned to control levels. Squibb et al. (1980) used a different dosing regimen to evaluate the behavioral effects of TET. With repeated exposures of either 0, 1, or 2 mg/kg (po) to adult rats, dose-related decreases in both forelimb and hindlimb grip strength were seen. As with motor activity, recovery appeared to be complete by 4 wk after dosing. The landing-foot spread technique of Edwards and Parker (1977) indicated similar neuromotor impairment and recovery (Reiter et al., 1980).

The startle response to both acoustic (Reiter et al., 1980; Squibb et al., 1980) and tactile (air-puff) stimuli (Squibb et al., 1980) was reduced during exposure to TET; these effects were also reversible on termination of exposure. Since the motor component of the startle reflex is the same for both acoustic and tactile stimuli, the reduction in startle amplitude to both stimuli probably reflects neuromuscular weakness. Additional data of Fechter et al. (1982) indicated that 30 ppm TET in the drinking

water, an exposure level specifically chosen to produce motor dysfunction, reduced acoustic startle responding but did not produce a shift in auditory thresholds. These data support the conclusion that reduced startle responding does not reflect specific sensory impairment. Tilson and Burne (1981) reported a similar conclusion for pain sensitivity. Responsiveness to painful stimuli was impaired during tail-flick and hot-plate testing but not on an operant shock titration procedure requiring a nose-poke response. However, while the tail-flick and hot-plate responses required large motor movements, the nose-poke response required only a small head movement. Recovery was seen by 2 weeks after dosing.

Both operant performance, conditioned flavor aversion, and active avoidance learning have been assessed in TET-exposed animals. Operant response rates on both fixed-interval and fixed-ratio schedules of reinforcement were reduced when TET was injected in rats immediately before the test session (DeHaven et al., 1982). Conditioned flavor aversions have been consistently reported following acute and repeated exposures to TET (Leander and Gau, 1980; MacPhail, 1982). When mice were exposed to 2 mg/kg TET for 27 days and active avoidance training was begun 2 days after the end of dosing (Gerren et al., 1976), no impairment was seen in the ability of mice to turn a wheel to avoid footshock. Interestingly, while there was no difference in

the total number of wheel turns between control and TET-exposed mice, spontaneous activity, measured daily 24 hr after dosing, was decreased by approximately 65% in TET-exposed mice. However, when shock avoidance was contingent on motor activity, TET animals were able to compensate for motor impairment.

To summarize, TET exposure produces decreases in motor activity, grip strength, operant response rates and startle response amplitudes as well as conditioned flavor aversions. These effects are generally reversible 2-4 weeks after the termination of exposure. TET does not appear to affect acquisition of an active avoidance task or the threshold to pain.

BEHAVIORAL EFFECTS OF TMT

Swartzwelder et al. (1981) reported that rats dosed with 7 mg/kg TMT were three times more active than controls when tested in an open field 40 days after exposure. Locomotor activity was also assessed in figure-eight mazes at several time points following a single exposure to 0, 5, 6 or 7 mg/kg TMT (Ruppert et al., 1982). There were no differences in activity 2 hr after dosing, but animals given 7 mg/kg TMT became progressively hyperactive from day 4 to day 16 after dosing. This time course parallels the development of limbic system damage, which first appears 2

days after dosing and becomes maximal within 3 weeks (Brown et al., 1979). These data illustrate both the steep nature of the dose-effect curve for TMT (no change in activity was seen at 5 or 6 mg/kg TMT) and the persistence of TMT toxicity (animals remained hyperactive 50 days after dosing).

Performance of a previously learned task (radial arm maze) and learning of new tasks (Hebb-Williams mazes, active and passive avoidance) have also been shown to be impaired by TMT. In a study by Walsh et al. (1982b), rats previously trained to perform a radial arm maze task were intubated with 0 or 6 mg/kg TMT. Animals routinely maximize accuracy on this task, by entering all baited arms, while avoiding arms which have been previously entered, until all reinforcers are obtained. TMT-treated animals were less accurate in selecting arms of the maze which still contained food, and required more arm entries to obtain all reinforcers; this deficit in performance persisted for at least 70 days after dosing. Although hyperactivity can be a confounding factor in interpreting learning and performance deficits, there were no differences in activity between groups on the radial arm maze 15-35 days after dosing.

Swartzwelder et al. (1982) also evaluated the effects of TMT exposure on performance in a Hebb-Williams maze. Animals receiving 7 mg/kg TMT made more errors than controls and also made more perseverative responses, repeatedly

entering blind alleys which did not lead to rein'orcement. In a subsequent study from this same laboratory, alcohol consumption was reduced in rats tested 21 and 150 days following 7 mg/kg TMT (Myers et al., 1982). TMT exposure has also been shown to impair retention of a passive avoidance task (Walsh et al., 1982a) and to facilitate active avoidance performance (Mactutus et al., 1982). These data are consistent in indicating that TMT exposure impairs acquisition and/or performance of tasks involving learning and memory.

Schedule-controlled performance is also affected by TMT exposure. Response rates on a schedule with increasing fixed-ratio requirements were increased by TMT (Schwartzwelder et al., 1981); this effect was directly related to the ratio requirements. In contrast, Wenger et al. (1982) reported a decreased rate of responding in TMT-exposed mice performing on a multiple fixed-ratio, fixed-interval schedule of reinforcement. Although a species or schedule difference could account for this discrepancy, the time of testing relative to exposure is probably a key factor contributing to this difference. Mice were tested by Wenger et al. during the acute phase of intoxication, 3-51 hours after dosing, while rats were tested by Swartzwelder et al. at least 40 days after dosing.

Studies are needed to evaluate the cumulative toxicity

of TMT. MacPhail (1982), for example, showed that the dosages required to produce conditioned flavor aversion were less following repeated administration of TMT than following a single dosage.

In summary TMT produces locomotor hyperactivity, deficits in learning and memory, conditioned flavor aversions and changes in operant response rates. These effects persist after a single exposure to TMT, and appear to be irreversible.

CONCLUSIONS

TET and TMT produce contrasting behavioral effects in adults which probably reflect differences in their effects on the nervous system. Both TET and TMT have been used as model compounds to investigate nervous system structure and function after defined neurotoxic insult. TET has been studied as a model of cerebral edema and neurodegenerative disorders, while TMT has been proposed as a model of hippocampal lesions, minimal brain dysfunction, the septal syndrome and kainic acid neurotoxicity. While these latter categorizations may be useful in guiding future research, they should not be allowed to constrict our viewpoint. For example, dramatic decreases in startle responding produced by TMT appear to reflect an ototoxic effect (Howell et al., 1982; Reiter et al., 1983; and Young and Fechter, 1983)

and, therefore, a complete understanding of the behavioral toxicity of this intriguing compound awaits further research.

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